REMARKS

Claims 1-15 were pending in the above-identified patent application. Applicants have amended claims 1, 2, 4-5, 7-11, and 13-14. Applicants have not added any claims and have canceled claims 3, 12, and 15. Accordingly, claims 1, 2, 4-11 and 13-14 are present for further examination.

In view of the following discussion, applicants respectfully request that the Examiner reconsider and withdraw the rejections made in the outstanding Office Action.

Support for the Amendments

Applicants have amended the claims in order to more clearly describe and distinctly claim the subject matter of applicants' novel crystalline polymorph Form-VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (Olanzapine). Specifically, applicants have canceled claim 3 and incorporated the subject matter therein into claim 1. Amended claim 1 now recites a crystalline polymorph Form-VI of Olanzapine "having an X-ray powder diffraction pattern substantially as depicted in Figure 1." Applicants have also incorporated the subject matter of claim 3 into claims 8, 13, and 14.

Applicants have also amended claims 2, 4-5, 7, 9, and 10-11 to correct certain minor procedural language.

These amendments to the claims are fully supported in the specification as originally filed, and thus no new matter is introduced by these amendments in accordance with 35 U.S.C. § 132. Accordingly, applicants request entry of these amendments.

Priority

The Examiner states that any non-provisional application claiming the benefit of one or more prior filed co-pending non-provisional applications or international applications designating the United States of America must contain or be amended to

contain in the first sentence of the specification following the title a reference to each such prior application, identifying it by application number or international application number and international filing date and indicating the relationship of the applications.

In accordance with the Examiner's suggestion, applicants have amended the specification to recite as follows: "This application is a national stage entry under 35 U.S.C. § 371 of PCT/US03/12414, filed April 22, 2003".

Rejection of Claims 10-15 under 35 U.S.C. § 112, first paragraph.

The Examiner has rejected claims 10-15 under 35 U.S.C. §112, first paragraph, on the basis that the specification, while being enabling for schizophrenia and bipolar disorder, does not reasonably provide enablement for any and all central nervous system (CNS) disorders. The Examiner states that the factors to be considered include: 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The Examiner states that the claims recite 2-methyl-10-(4-methyl-1-piperazinyl)-4H-thieno[2,3-b][1,5]benzodiazepine and claims 12-15 provide a composition for the treatment of disorders of the central nervous system. The Examiner states that the central nervous system disorders of claims 12-15 are not described in the specification. Applicants traverse the Examiner's rejection.

As noted above, claims 12 and 15 have been canceled.

Applicants' claim 10, as amended, recites a "composition comprising crystalline Form-VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine according to any one of claims 1, 2, and 4-7 and a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, binder, stabilizer, solvent or solvate." Claim 11, dependent from claim 10, recites the composition "in the form of a tablet, capsule, lozenge, powder, syrup, solution, suspension, ointment, or dragée." Neither claim 10 nor claim 11 specifically refers to disorders of the central nervous system.

Applicants' claim 13, as amended, recites a "method for treating a disorder of the central nervous system comprising administering an effective amount of crystalline

Form-VI of 2-methyl-4-1(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine according to any one of claims 1, 2, and 4-7 and a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, binder, stabilizer, solvent or solvate to a patient in need thereof, wherein the crystalline polymorph Form-VI of Olanzapine has an X-ray powder diffraction pattern substantially as depicted in Figure 1."

Applicants' claim 14, as amended, recites a "composition for the treatment of a disorder of the central nervous system comprising an effective amount of crystalline Form-VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine according to any one of claims 1, 2, and 4-7 wherein the crystalline polymorph Form-VI of Olanzapine has an X-ray powder diffraction pattern substantially as depicted in Figure 1."

Contrary to the Examiner's position, applicants submit that the present specification does disclose the use of the subject compound for the treatment of disorders of the central nervous system at, for example, page 1, lines 15-19.

> The present invention also relates to compositions made using the crystalline form of 2-methyl-4-(4-methyl-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine and the use of crystalline form and compositions made using the crystalline form for the treatment of disorders of the central nervous system, for treating psychotic patients and mild anxiety.

Applicants' specification further discloses the use of the subject compound at, for example, page 1, lines 21-23.

> U.S. 5,229,382 discloses the preparation of Olanzapine and its acid addition salts, having pharmaceutical properties, particularly in the treatment of disorders of the central nervous system.

U.S. 5,229,382 (*Chakrabarti et al.*) states that the "compound of the invention has given surprising and excellent results, described in greater detail below, in experimental screens for testing activity on the central nervous system and in clinical trials, which results indicate its usefulness for the relatively safe and effective treatment of a wide range of disorders of the central nervous system." (*Chakrabarti et al.* at col. 2, lines 38-45.)

Accordingly, applicants' specification does provide enablement for the treatment of central nervous system disorders. Hence, the Examiner's rejection of claims 10, 11. 13, and 14 under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Rejection of Claims 2, 8-12, 14, and 15 under 35 U.S.C. § 112, second paragraph.

The Examiner has rejected claims 2, 8-12, 14 and 15 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner states the following: a) claim 2 is vague because it is not known what is meant by the period which appears at the end of the third line indicating the end of the claim; b) claims 8 and 10 are vague because it is not known what is meant by "novel"; c) there is no antecedent basis in claim 9 for the limitation of "said alcohol"; d) claim 11 is vague because it is not known what is meant by “dragee”; e) claim 12 is a substantial duplicate of claim 10 or 11; f) claim 14 is vague because the terminology "a medicine" does not clarify whether the claim is limited to a compound, composition, or even complex composition; g) claim 15 provides for the use of the crystalline Form-VI, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. Applicants' claims, as amended, obviate the Examiner's rejection.

Applicants' response to the Examiner's rejections are set out below.

a) Applicants have deleted the period in the third line of claim 2 and substituted therefor a colon; the period has been placed after the table.

b) Applicants have deleted "novel" in claims 8 and 10.

c) Applicants have deleted "said alcohol" in claim 9 and substituted therefore "C_1-C_6 alkanol".

d) Applicants have deleted the word "dragee" in claim 11 and substituted therefore the word "dragée", which means a small medicated confection (see the attached page from the internet version of *American Heritage Dictionary of the English Language, Fourth Edition*).

e) Applicants have deleted claim 12.

f) Applicants have deleted the word "medicine" in claim 14 and substituted therefore the word "composition".

g) Applicants have deleted claim 15.

Hence, the Examiner's rejection of claims 2, 8-11, and 14 under 35 U.S.C. §12, second paragraph, should be withdrawn.

Rejection of Claim 15 under 35 U.S.C. § 101

The Examiner has rejected claim 15 under 35 U.S.C. §101 on the basis that the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process. Applicants' claim, as amended, obviates the Examiner's rejection.

As set out above, applicants have deleted claim 15. Hence, the Examiner's rejection of claim 15 under 35 U.S.C. § 101 should not be maintained.

Rejection of Claims 1, 8 and 10-15 under 35 U.S.C. § 102(b) as being anticipated by *Beasley et al.'963*

The Examiner has rejected claims 1, 8 and 10-15 under 35 U.S.C. §102(b) as being anticipated by United States patent no. 6,159,963 (*Beasley et al.'963).* The Examiner states that *Beasley et al.'963* teaches the compounds, compositions and method of use and process of preparing the compounds of the instant invention where Olanzapine is mixed with methanol at 20°C for 30 minutes and dried at 45°C overnight as shown in Preparation 1. Applicants' claims, as amended, obviate the Examiner's rejections.

As set out above, applicants have canceled claim 3 and incorporated the subject matter therein into claim 1. Amended claim 1 now recites a "crystalline polymorph Form-VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (Olanzapine), having an X-ray powder diffraction pattern substantially as depicted in Figure 1."

Applicants have also incorporated the subject matter of claim 3 into claim 8. Amended claim 8 now recites a "process for the preparation of a crystalline polymorph Form-VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (Olanzapine), having an X-ray powder diffraction pattern substantially as depicted in Figure 1, which comprises; (i) stirring polymorph Form-I of Olanzapine in a C_1-C_6 alkanol at a temperature of 0 to 40°C for 30 minutes to 10 hours; (ii) isolating the obtained solid form step (i) by conventional methods; and (iii) drying the compound of step (ii) at a temperature of 40 to 100°C to afford the desired crystalline polymorph Form-VI of Olanzapine."

Applicants have also incorporated the subject matter of claim 3 into claim 10. Amended claim 10 now recites a "composition comprising crystalline Form-VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine according to any one of claims 1, 2, and 4-7 and a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, binder, stabilizer, solvent or solvate."

Applicants have also incorporated the subject matter of claim 3 into claim 13. Amended claim 13 now recites a "method for treating a disorder of the central nervous system comprising administering an effective amount of crystalline Form-VI of 2-methyl-4-1(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine according to any one of claims 1, 2, and 4-7 and a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, binder, stabilizer, solvent or solvate to a patient in need thereof, wherein the crystalline polymorph Form-VI of Olanzapine has an X-ray powder diffraction pattern substantially as depicted in Figure 1."

Applicants have also incorporated the subject matter of claim 3 into claim 14. Amended claim 14 now recites a "composition for the treatment of a disorder of the central nervous system comprising an effective amount of crystalline Form-VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine according to any one of claims 1, 2, and 4-7 wherein the crystalline polymorph Form-VI of Olanzapine has an X-ray powder diffraction pattern substantially as depicted in Figure 1."

The *Beasley et al.'963* reference discloses a method for treating substance abuse comprising administering an effective amount of Olanzapine or a

pharmaceutically acceptable salt thereof to a patient in need thereof. In preparation 1, *Beasley et al.'963* states that technical grade Olanzapine was prepared by conventional methods with the product mixture admixed with methanol with stirring at 20°C. for 30 minutes. Three volumes of water were then added and the reaction slurry cooled to 0-5°C. with stirring for 30 minutes and the product filtered. In preparation 2, *Beasley et al.'963* states that technical grade Olanzapine was converted to Form II of the Olanzapine polymorph by suspending technical grade Olanzapine in ethyl acetate, heating to 76°C. for 30 minutes, cooling to 25°C., and filtering the mixture.

Applicants submit that *Beasley et al.'963* does not anticipate applicants' claims. *Beasley et al.'963* discloses a process for preparing technical grade Olanzapine from a solution in methanol with precipitation with water and a process for preparing Form II of the Olanzapine polymorph by precipitation of technical grade Olanzapine in ethyl acetate. Applicants' process for the preparation of a crystalline polymorph Form-VI of Olanzapine includes stirring polymorph Form-I of Olanzapine in a C_1-C_6 alkanol at a temperature of 0 to 40°C for 30 minutes to 10 hours and isolating the solid form by conventional methods. *Beasley et al.'963* also does not disclose a crystalline polymorph Form-VI of Olanzapine having an X-ray powder diffraction pattern substantially as shown in Figure 1. In summary, *Beasley et al.'963* does not teach each and every element of applicants' crystalline polymorph Form-VI of Olanzapine. Accordingly, *Beasley et al.'963* does not anticipate applicants' claims under 35 U.S.C. §102(b).

Polymorphs arise when molecules of a compound arrange in the solid state in distinct ways. By varying the temperature of the solution and using different solvents, different polymorphs can be formed. Although identical in chemical composition, polymorphs can have very different properties. Polymorphs are distinguishable by various analytical techniques, especially X-ray powder diffraction patterns.

Under 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in the prior art. *Akzo N.V. v. U.S. International Trade Commission*, 1 USPQ 2d 1241, 1245 (Fed. Cir. 1986), cert. denied, 482 U.S. 909 (1987). Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *W.L. Gore & Associates v. Garlock, Inc.*, 220

USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 221 USPQ 481, 485 (Fed. Cir. 1984) (emphasis added). We think the precise language of 35 U.S.C. § 102 that "a person shall be entitled to a patent unless," concerning novelty and unobviousness, clearly places a burden of proof on the Patent Office which requires it to produce the factual basis for its rejection of an application under § 102 and § 103. *In re Warner*, 154 USPQ 173, 177 (C.C.P.A. 1967), cert. denied, 389 U.S. 1057 (1968).

Hence, the Examiner's rejection of claims 1, 8, 10, and 11-14 under 35 U.S.C. § 102(b) as being anticipated by *Beasley et al.'963* should be withdrawn.

Rejection of Claims 1, 8-15 under 35 U.S.C. § 102(b) as being anticipated by *Beasley et al.'928*

The Examiner has rejected claims 1 and 8-15 under 35 U.S.C. § 102(b) as being anticipated by United States Patent No. 5,776,928 (*Beasley et al.'928).* The Examiner states that *Beasley et al.'928* teaches the compounds, compositions and method of use and process of preparing the compounds of the instant invention where Olanzapine is mixed with t-butanol. Applicants' claims, as amended, obviate the Examiner's rejections.

As set out above, applicants have incorporated the subject matter of claim 3 into claims 1, 3, 10, 13, and 14.

The *Beasley et al.'928* reference discloses a method for treating dyskinesias comprising administering an effective amount of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thienol[2,3-b][1,5]benzodiazepine. In preparation 8, *Beasley et al.'928* states that Form I of Olanzapine was prepared from a technical grade of Olanzapine by suspension of the compound in *tert*-butanol at 60°C. for 30 minutes followed by cooling and filtration.

Applicants submit that *Beasley et al.'928* does not anticipate applicants' claims. *Beasley et al.'928* discloses a process for preparing Form I of Olanzapine by

suspending technical grade Olanzapine from a solution in *tert*-butanol at 60°C. for 30 minutes followed by cooling and filtration. Applicants' process for the preparation of a crystalline polymorph Form-VI of Olanzapine includes stirring polymorph Form-I of Olanzapine in a C_1-C_6 alkanol at a temperature of 0 to 40°C for 30 minutes to 10 hours and isolating the solid form by conventional methods. *Beasley et al.'928* also does not disclose a crystalline polymorph Form-VI of Olanzapine having an X-ray powder diffraction pattern substantially as shown in Figure 1. In summary, *Beasley et al.'928* does not teach each and every element of applicants' crystalline polymorph Form-VI of Olanzapine. Accordingly, *Beasley et al.'928* does not anticipate applicants' claims under 35 U.S.C. §102(b).

Hence, the Examiner's rejection of claims 1, 8-11, 13, and 14 under 35 U.S.C. §102(b) as being anticipated by *Beasley et al.'928* should be withdrawn.

Rejection of Claims 1 and 10-15 under 35 U.S.C. § 102(b) as being anticipated by *Bunnell*

The Examiner has rejected claims 1 and 10-15 under 35 U.S.C. § 102(b) as being anticipated by United States Patent No. 5,631,250 (*Bunnell).* The Examiner states that *Bunnell* teaches the compounds, compositions and method of use and process of preparing the compounds of the instant invention where Olanzapine is mixed with methanol, ethanol and 1-propanol. Applicants' claims, as amended, obviate the Examiner's rejections.

As set out above, applicants have incorporated the subject matter of claim 3 into claims 1, 3, 10, 13, and 14.

The *Bunnell* reference discloses processes for making lower alcohol solvates of Olanzapine. In *Bunnell,* Example 1 discloses the preparation of Form-1 from methanolate by mixing a powder sample of methanol solvate with a powder sample of Form-1 Olanzapine; Example 2 discloses the preparation of methanol solvate by admixing crude Olanzapine with ethyl acetate and methanol (8:2) at ambient temperature for 10 days; Example 3 discloses the preparation of methanol solvate by contacting crude Olanzapine with a 1:1 mixture of methanol and water and heating the

mixture to 78°C for 30 minutes; Example 4 discloses the preparation of ethanol solvate by suspending crude Olanzapine in absolute ethanol at 60°C. for 30 minutes; Example 5 discloses the preparation of ethanol solvate by suspending crude Olanzapine in a mixture of ethanol and water (95:5) and heating to 60°C. for 30 minutes; Example 6 discloses the preparation of 1-propanol solvate by suspending crude Olanzapine in 1-propanol at 70°C. for 30 minutes; Example 7 discloses the preparation of technical grade Olanzapine by contacting crude Olanzapine with a 1:1 mixture of methanol and water at 78°C. for 30 minutes; Example 8 discloses the preparation of technical grade Olanzapine by suspending crude Olanzapine in absolute ethanol at 60°C. for 30 minutes; Example 9 discloses the preparation of technical grade Olanzapine by suspending crude Olanzapine in 1-propanol at 70°C. for 30 minutes; and Example 10 discloses the synthesis of technical grade Olanzapine according to known procedures and purifying the product by admixture with methanol at 20°C. for 30 minutes followed by addition of 3 volumes of water.

Applicants submit that *Bunnell* does not anticipate applicants' claims. None of the methods disclosed by *Bunnell* for preparing lower alcohol solvates of Form-I of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (Olanzapine) teaches or suggests applicants' process for preparing crystalline polymorph Form-VI of Olanzapine. Applicants' process for preparing crystalline polymorph Form-VI of Olanzapine includes stirring polymorph Form-I of Olanzapine in a C_1-C_6 alkanol at a temperature of 0 to 40°C for 30 minutes to 10 hours and isolating the solid form by conventional methods. *Bunnell* also does not disclose a crystalline polymorph Form-VI of Olanzapine having an X-ray powder diffraction pattern substantially as shown in Figure 1. In summary, *Bunnell* does not teach each and every element of applicants' crystalline polymorph Form-VI of Olanzapine. Accordingly, *Bunnell* does not anticipate applicants' claims under 35 U.S.C. § 102(b).

Hence, the Examiner's rejection of claims 1, 10, 11, 13 and 14 under 35 U.S.C. § 102(b) as being anticipated by *Bunnell* should be withdrawn.

Rejection of Claims 10-12 under 35 U.S.C. § 102(b) as being anticipated by *Chakrabarti et al.*

The Examiner has rejected claims 10-12 under 35 U.S.C. § 102(b) as being anticipated by United States Patent No. 5,229,382 (*Chakrabarti et al.*). The Examiner states that *Chakrabarti et al.* teaches the compositions of 2-methyl-10-(4-methyl-1-piperazinyl)-4H-thieno[2,3-b][1,5]benzodiazepine as taught in column 3, lines 30-31. Applicants' claims, as amended, obviate the Examiner's rejections.

As set out above, applicants have incorporated the subject matter of claim 3 into claims 1, 3, 10, 13, and 14.

The *Chakrabarti et al.* reference discloses 2-methyl-10-(4-methyl-1-piperazinyl)-4H-thieno-[2,3-b][1,.5]benzodiazepine having pharmaceutical properties of particular use in the treatment of disorders of the central nervous system. *Chakrabarti et al.* discloses at column 3, lines 29-35

> In dog toxicity studies with a closely analogous compound, 2-ethyl-10-(4-methyl-1-piperazinyl)-4H-thieno[2,3-b]-[1,5]benzodiazepine, at a dosage of 8 mg/kg, it was observed that four out of eight dogs showed a significant rise in cholesterol levels, whereas the compound of the invention did not show any rise in cholesterol levels.

Applicants submit that *Chakrabarti et al.* does not anticipate applicants' claims. *Chakrabarti et al.* does not teach or suggest applicants' process for preparing crystalline polymorph Form-VI of Olanzapine. Applicants' process for preparing crystalline polymorph Form-VI of Olanzapine includes stirring polymorph Form-I of Olanzapine in a C_1-C_6 alkanol at a temperature of 0 to 40°C for 30 minutes to 10 hours and isolating the solid form by conventional methods. *Chakrabarti et al.* also does not disclose a crystalline polymorph Form-VI of Olanzapine having an X-ray powder diffraction pattern substantially as shown in Figure 1. In summary, *Chakrabarti et al.* does not teach each and every element of applicants' crystalline polymorph Form-VI of Olanzapine. Accordingly, *Chakrabarti et al.* does not anticipate applicants' claims under 35 U.S.C. §102(b).

Hence, the Examiner's rejection of claims 10 and 11 under 35 U.S.C. § 102(b) as being anticipated by *Chakrabarti et al.* should be withdrawn.

Objection to Claim 12

The Examiner has objected to claim 12 under 37 C.F.R. § 1.75(c) as being in improper form because a multiple dependent claim must not be dependent on another multiple dependent claim. Applicants' claims, as amended, obviate the Examiner's rejections.

As set out above, applicants have canceled claim 12. Hence, the Examiner's objection to claim 12 should be withdrawn.

Information Disclosure Statement

To complete the record of this application, applicants are submitting a Form PTO-1449 substitute, listing the four documents that were cited in the International Search Report. Copies of the three listed non-U.S. patent documents are also enclosed. Please return a copy of the form with the next communication to indicate that these documents have been made of record.

SUMMARY

In view of the foregoing Amendment and Response, applicants request reconsideration pursuant to 37 C.F.R. § 112 and allowance of the claims pending in this application. Applicants request the Examiner to telephone the undersigned attorney should the Examiner have any questions or comments, which might be most expeditiously handled by a telephone conference. If any additional fee is required in

connection with this submission, authorization is hereby given to charge the amount of such fee to Deposit Account No. 50-3221.

Respectfully submitted,

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The American Heritage® Dictionary of the English Language: Fourth Edition. 2000.

dragée

SYLLABICATION: dra·gée

PRONUNCIATION: drä-zhā'

NOUN: **1.** A small, often medicated candy. **2.** A tiny, hard candy used to decorate baked goods.

ETYMOLOGY: French, from Old French *dragie*. See dredge[2].